TECHNIQUES D'HISTOLOGIE ET DE BIOLOGIE MOLECULAIRE DES METASTASES OSSEUSES DES CANCERS BRONCHO-PULMONAIRES

Les métastases osseuses survenant dans 30 à 50% des adénocarcinomes pulmonaires (5), elles peuvent être biopsiées sous scanner en vue d'obtenir un diagnostic histologique et moléculaire (10). Ce choix sera privilégié chez un patient fragile chez qui la fibroscopie ou la ponction transpariétale sont risquées ou bien si ces examens n'ont pas permis d'obtenir un diagnostic à partir de la tumeur primitive. De localisation pelvienne ou rachidienne le plus souvent, les métastases osseuses sont facilement accessibles par un radiologue entraîné.

1. Quel site biopsier ?

Les biopsies sous scanner doivent intéresser la zone frontière entre la tumeur et l'os, cela afin d'éviter les zones nécrotiques habituellement situées au centre de la lésion. Le rendement est alors excellent et permet d'obtenir du matériel tumoral dans plus de 90% des cas (10). Le nombre de fragments, la taille et la longueur de ces fragments sont bien sûr garants de la quantité de matériel recueilli. Généralement deux biopsies d'environ 1 cm et d'une taille de 14 G sont suffisantes pour permettre les diagnostics histologiques et moléculaires.

2. Comment conditionner les biopsies osseuses sur le plan anatomo-pathologique ?

Les biopsies doivent être rapidement fixées au formol tamponné pendant une durée d'au minimum 6 heures. Si une décalcification est nécessaire, celle-ci doit être réalisée via l'EDTA, chélateur de calcium [0,5M EDTA, (pH 8,0) *Molecular Biology Grade*] ou via l'acide formique (acide faible qui permet la conservation de l'ADN) et toujours après fixation complète au formol tamponné. La décalcification via l'EDTA/acide formique est plus longue qu'en utilisant un décalcifiant classique à base d'acide fort (acide nitrique notamment), cependant elle est indispensable afin de conserver l'intégrité de l'ADN et donc de réaliser les techniques de biologie moléculaire et d'hybridation *in situ*. Cette décalcification est réalisée après fixation au formol tamponné en plaçant la biopsie dans quelques mL d'EDTA non dilué ou d'acide formique. Des cycles fixation/décalcification de 2 à 4 heures doivent alors être réalisés, durant le temps nécessaire (quelques heures à un ou deux jours selon le degré de calcification et la taille de l'échantillon). Si la biopsie n'est pas suffisamment décalcifiée le vendredi soir, ne pas la laisser dans le décalcifiant tout le week-end, mais la replacer dans le formol tamponné et recommencer les cycles de décalcification dès le lundi matin. Après décalcification, chaque biopsie est alors mise en cassette et incluse selon les techniques habituelles, en évitant, à chaque étape de l'inclusion, le contact avec des agents acides. Il est indispensable de vérifier le pH du formol utilisé pour la fixation, cela afin de contrôler la formation d'acide formique qui peut avoir lieu au cours du temps dans une solution de formol préparée à l'avance. En cas de biopsies multiples, il est recommandé de placer une biopsie par cassette, cela en vue de conserver un bloc pour les études immuno-histochimiques et un second bloc pour la biologie moléculaire et d'éviter ainsi une perte de matériel tumoral.

3. Quel est le rôle de l'immunohistochimie ?

L'étude immuno-histochimique permet d'orienter ou de confirmer l'origine primitive de la métastase. Elle sera à adapter selon les cas. En cas de forte suspicion de métastase de cancer pulmonaire (imagerie évocatrice, antécédent concordant etc.) et devant un aspect morphologique évocateur d'adénocarcinomes seuls, une expression de la cytokératine 7 et du TTF1 pourra être recherchée. Avec l'arrivée des immunothérapies, la recherche d'expression de PD-L1 par immunohistochimie fait maintenant partie de la routine pour tous les adénocarcinomes, les carcinomes épidermoïdes et les carcinomes sarcomatoïdes d'origine pulmonaire (*cf* partie histologie du CBNPC). La mise au point sur les métastases osseuses est en cours.

Si l'aspect morphologique est en faveur d'un carcinome indifférencié, le panel d'immunohistochimie pourra inclure en plus des anticorps suscités, l'anticorps p40 et une coloration spéciale bleu alcian afin de faire la différence entre un adénocarcinome et un carcinome épidermoïde. Si d'autres antécédents de tumeurs primitives ostéophiles sont connus, le panel d'immunohistochimie pourra alors inclure les anticorps anti-PSA, anti-récepteurs aux œstrogènes, à la progestérone et anti-cytokératine 20 (➔ Référentiel CBNPC).

4. Est-il possible de réaliser les techniques de biologie moléculaire sur les biopsies osseuses ?

Après confirmation du diagnostic de métastase osseuse de cancer pulmonaire, les techniques de biologie moléculaire et d'hybridation *in situ* pourront être réalisées selon les techniques habituelles par la plateforme régionale INCa. L'extraction d'ADN est réalisée après macro- ou microdissection laser afin d'augmenter la sensibilité des PCR. Les recommandations concernant le type de biomarqueurs à rechercher sur une métastase osseuse de cancer pulmonaire sont identiques aux recommandations faites sur les tumeurs primitives. Devant une métastase osseuse synchrone ayant permis le diagnostic histologique initial d'adénocarcinome pulmonaire, l'ensemble des biomarqueurs doit être recherché avec en priorité la recherche d'une mutation de l'EGFR et la recherche d'une translocation d'ALK. Si la biopsie est réalisée dans un contexte de résistance à un traitement inhibiteur de tyrosine kinase, les mutations de résistance devront être recherchées. En cas de diagnostic histologique de carcinome épidermoïde, aucune recherche moléculaire n'est recommandée à l'heure actuelle.

Recommandations

-L'ensemble des techniques de biologie moléculaire disponibles sur les tumeurs primitives est également disponible sur les métastases osseuses.
-Pour obtenir un ADN de qualité, il ne faut pas réaliser une décalcification à l'acide mais à l'EDTA.
-La biopsie osseuse sous scanner permet de ramener plusieurs « carottes » qui donnent un matériel généralement suffisant pour la recherche des différents biomarqueurs.
-La biopsie osseuse sous scanner est à réaliser à la périphérie de la lésion pour limiter le risque de tissu nécrotique inutilisable.

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